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Cervical carcinoma and reproductive factors: Collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies

International Collaboration of Epidemiological Studies of Cervical Cancer

The International Collaboration of Epidemiological Studies of Cervical Cancer has combined individual data on 11,161 women with invasive carcinoma, 5,402 women with cervical intraepithelial neoplasia (CIN)3/carcinoma *in situ* and 33,542 women without cervical carcinoma from 25 epidemiological studies. Relative risks (RRs) and 95% confidence intervals (CIs) of cervical carcinoma in relation to number of full-term pregnancies, and age at first full-term pregnancy, were calculated conditioning by study, age, lifetime number of sexual partners and age at first sexual intercourse. Number of full-term pregnancies was associated with a risk of invasive cervical carcinoma. After controlling for age at first full-term pregnancy, the RR for invasive cervical carcinoma among parous women was 1.76 (95% CI: 1.53–2.02) for ≥7 full-term pregnancies compared with 1–2. For CIN3/carcinoma *in situ*, no significant trend was found with increasing number of births after controlling for age at first full-term pregnancy among parous women. Early age at first full-term pregnancy was also associated with risk of both invasive cervical carcinoma and CIN3/carcinoma *in situ*. After controlling for number of full-term pregnancies, the RR for first full-term pregnancy at age <17 years compared with ≥25 years was 1.77 (95% CI: 1.42–2.23) for invasive cervical carcinoma, and 1.78 (95% CI: 1.26–2.51) for CIN3/carcinoma *in situ*. Results were similar in analyses restricted to high-risk human papilloma virus (HPV)-positive cases and controls. No relationship was found between cervical HPV positivity and number of full-term pregnancies, or age at first full-term pregnancy among controls. Differences in reproductive habits may have contributed to differences in cervical cancer incidence between developed and developing countries.

Key words: cervical carcinoma; cervical intraepithelial neoplasia; reproductive factors; full-term pregnancy; age at first full-term pregnancy; collaborative reanalysis; relative risk

Parity was one of the earliest risk factors to be associated with cancer risk. Already in 1842, on the basis of death certificates in Verona, Italy, Rigoni-Stern observed that cancers of the uterus (which at that time chiefly originated from the cervix) were more frequent in married women, who tended to be multiparous, whereas breast neoplasms were more common in nulliparae, including nuns.[1]

Epidemiological studies conducted in the 1950's and 1960's pointed to sexual habits, and subsequent studies to sexual infections, specifically high-risk human papillomavirus (HPV) types,[2] as the key factor in cervical carcinogenesis. Consequently, they tended to consider that the association between reproductive factors and cervical cancer was chiefly accounted for by confounding from sexual habits.[3–5] More recent studies, however, included detailed information on sexual behaviour[6] and on HPV infection[7] and lent support to the possibility that the effect of reproductive factors is not explained by the confounding effect of sexual habits or HPV infection.

The contribution of reproductive factors in cervical cancer aetiology has relevant public health implications as cervical cancer incidence is high in several developing countries where multiparity is still common.[8,9] The magnitude, however, of this contribution remains uncertain, as many studies reported only relatively narrow ranges of parity and age at first full-term pregnancy (FTP). In our study we analysed the relation between reproductive factors and cervical cancer using pooled data from 25 studies, including over 16,000 cases of invasive and pre-invasive carcinoma and 33,000 controls.

Material and methods

Identification of studies and collection of data

The International Collaboration of Epidemiological Studies of Cervical Cancer was set up primarily to study the effects of hormonal contraceptive use and other factors on the risk of cervical cancer. Epidemiological studies of invasive cervical carcinoma or cervical intraepithelial neoplasia (CIN)3/carcinoma *in situ* with information on hormonal contraceptive use and reproductive factors (number of FTPs and age at first FTP) were eligible for inclusion in this collaborative reanalysis. Cohort (prospective) studies were eligible if they included at least 30 cases of invasive cervical car-

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia; FCI, floating confidence interval; FTP, full-term pregnancy; HPV, human papillomavirus; RR, relative risk; WHO, World Health Organisation.

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cinoma or CIN3/carcinoma *in situ*, and case-control studies were eligible if they had at least 100 invasive cervical carcinoma cases or 200 CIN3/carcinoma *in situ* cases. Studies were identified from review articles, computer-aided literature searches and discussions with colleagues. Efforts were made to identify all studies that included relevant information, whether or not results on reproductive habits had been published. The principal investigators of all studies identified were invited to collaborate. A list of studies and references was given to collaborators and they were asked if they knew of further studies; the principal investigators of those studies were also invited to collaborate. Additional studies came to light as a result of these enquiries and, in view of the wide consultation, it seems unlikely that any substantial studies were missed. Analysis and presentation of the data were discussed by collaborators at the first meeting of the International Collaboration of Epidemiological Studies of Cervical Cancer in Lyon, France (November 2003), and subsequently.

Individual subject information was collected and analysed centrally to enable variables to be defined consistently across studies. Cohort studies were analysed as nested case-control studies with up to 4 randomly selected controls per case matched by age at diagnosis. Data on socioeconomic factors, cigarette smoking history, reproductive factors, sexual behaviour, hormonal and barrier contraceptive use and Pap smear history were collected as much as possible in a standard format. A measurement of HPV infection was included, whenever available.

Histological classification of cancers was performed according to the World Health Organisation (WHO) Classification of Tumours for neoplasms of the uterine cervix,[10] using, whenever possible, the original International Classification of Disease codes reported for each woman. Invasive tumours, including those reported as micro-invasive, were classed as follows: squamous cell carcinoma, adenocarcinoma (including adenosquamous carcinoma), other types for which histology was available (including unspecified epithelial cancers, multiple types *e.g.*, squamous cell with adenocarcinoma and rare specified tumours) or 'histology unknown'. CIN3/carcinoma *in situ* included mainly squamous/unspecified *in situ* and a few specified cases of adenocarcinoma *in situ*. When invasive carcinoma and CIN3/carcinoma *in situ* were both present, the carcinoma was classified as invasive. Benign and secondary cervical tumours, lesions classed as CIN1 or CIN2, and mesenchymal, mixed epithelial/mesenchymal, melanocytic, germ cell and lymphoid/haematopoetic neoplasms were excluded.

Information on the number of FTPs and age at first FTP had been collected in comparable ways in all studies, or could be derived simply, so that use of similar definitions (*i.e.*, a pregnancy that lasted $\geq$26 weeks) across studies was generally possible. Information on history of abortion was available for 20 studies, but the accuracy of the reported number and, notably, the distinction between voluntary and spontaneous abortions was uncertain and hence this variable could not be considered. Twelve studies had information on type of delivery (vaginal or caesarean).

Controls who had had a hysterectomy were excluded, when this information was reported, as were women who reported no previous sexual partners (27 cases and 2,324 controls). When considering the number of Pap smears reported, smears taken within 1 year of the date of diagnosis, or within 1 year of interview for control women, were excluded. This was possible in most studies, and should reduce the chance of counting diagnostic smears as screening smears.

Additional analyses were performed for studies that provided a measure of cervical high-risk HPV infection in exfoliated cells or biopsies using polymerase chain reaction. These analyses included: (1) comparison of high-risk HPV-positive and high-risk HPV-negative control women in order to evaluate the association between reproductive factors and HPV infection among women without cervical cancer, and (2) re-evaluation of reproductive factors among high-risk HPV-positive cervical carcinoma cases and high-risk HPV-positive control women only, in order to evaluate the possible effect of reproductive factors on invasive cervical carcinoma among high-risk HPV-positive women. All the studies included tests for HPV16 and 18 at least. HPV types were considered as high-risk types according to Muñoz *et al*.[11] Women who were positive for low-risk HPV types only were combined with HPV-negative women.

Statistical methods and presentation of data

Conditional logistic regression was used to calculate relative risks (RRs) and their corresponding 95% confidence intervals (CIs). When more than 2 groups were compared, 95% CIs in figures were calculated using floating absolute risks[12,13] to allow valid comparisons between any 2 groups, and these are referred to as 95% floating confidence intervals (FCIs). The use of floating absolute risks does not alter the RRs, but slightly reduces the variances of the RRs that are not defined as 1.0, and also reduces unwanted covariances between them. However, the conventional 95% CIs are presented in the text. Tests for linear trend of the RRs for the present analyses were performed, when appropriate, giving an increasing score for each level of the categorised variable and fitting them in the model as continuous variables. Heterogeneity tests were carried out by calculating the likelihood ratio between 2 models: one in which the effect of the risk factor of interest was allowed to vary between strata, and another where it was constrained to be the same across strata.

Women were stratified by study, or by centre in multi-centric studies (Brinton, WHO, IARC, Table I) and by single year of age, to ensure that comparisons were made between women of the same age from the same population. In the comparison of findings between individual studies or types of study design, a trend model was used for number of FTPs and age at first FTP, and the RR was computed by 1-FTP increase and 1-year decrease in age at first FTP, respectively. Of several potential confounding factors, sexual habits are particularly important. Analyses were stratified for lifetime number of sexual partners (1, 2–5, 6+) and age at first sexual intercourse (<17, 17–18, 19–21, 22+ years). Additional inclusion of these 2 variables as continuous variables did not materially modify any of the results. Likewise, information on other factors, such as educational level, cigarette smoking, hormonal contraceptive use and history of Pap smear did not appreciably modify any of the results. Consequently these factors were not controlled for in most analyses, but were used for stratum-specific RRs.

Presentation of results

Results in the text are presented as RRs and their corresponding 95% CIs. Where results are presented in the form of plots, RRs are represented by squares and their corresponding 95% CIs or FCIs by horizontal lines. The position of the square indicates the point estimate of the RR, and the area of the square is inversely proportional to the variance of the logarithm of the RR, thus providing an indication of the amount of information available for that particular estimate. Where summary RRs have been calculated, these are shown as open diamonds, whose horizontal extent indicates the 95% CI. On the plots, the numbers of cases and controls given in each category are the numbers for which information was available for that category; the amount of information available for the estimation of the RR by conditional logistic regression reflects the number of discordant cases and controls in each stratum, and therefore will always be smaller than the total number of cases and controls.

Results

Data could not be retrieved for 10 published studies[14–24] and 1 research group[25] declined to take part in the collaboration. Of the studies identified, original data were available from 25,[6,26–61] and all had information on reproductive factors and were therefore included in the present collaborative reanalysis (Table I). The studies included 9 cohort and 16 case-control studies. Five studies

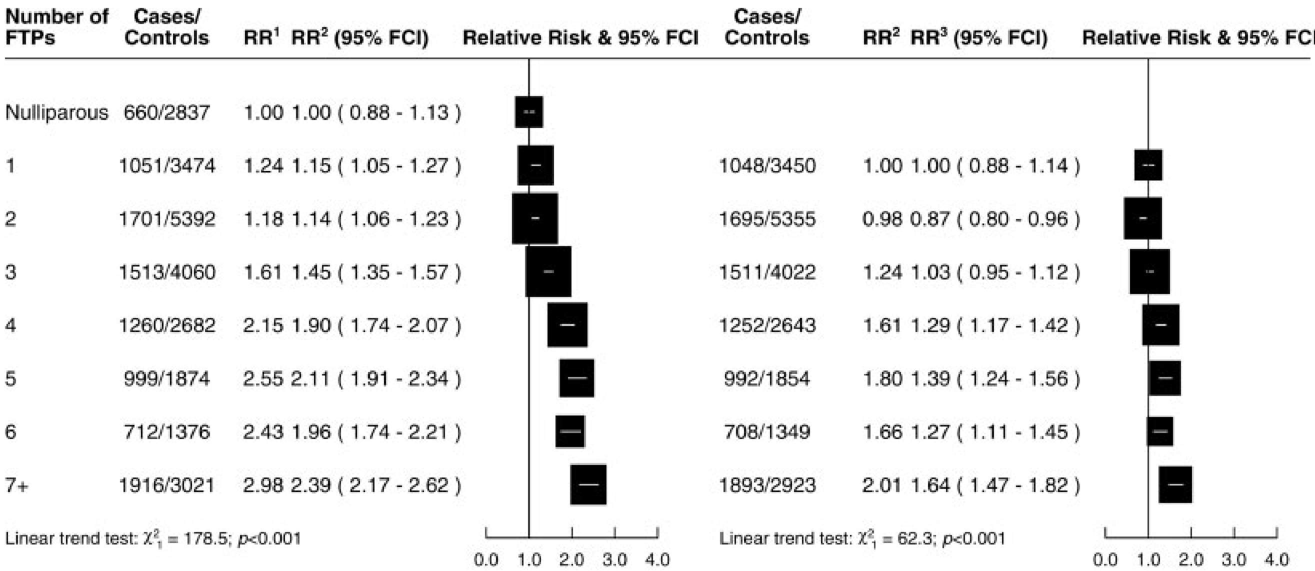
TABLE I – CHARACTERISTICS OF CASES OF INVASIVE CERVICAL CARCINOMA AND CIN3/CARCINOMA *IN SITU* AND CONTROLS BY STUDY TYPE AND STUDY DESIGN

Study name–reference	Country	Cases		Controls	Median year of diagnosis	Median age of diagnosis	HPV method
		Invasive	*In situ*				
Cohort							
RCGP[26]	UK	162	0	609	1980	42	None
Oxford FPA[27]	UK	42	0	154	1983	39	None
Tromsφ[28]	Norway	0	198	815	1986	32	None
Sweden[29]	Sweden	0	378	378	1987	34	PCR
Manchester[30]	UK	0	199	181	1990	32	PCR
Portland Kaiser[31]	USA	0	69	263	1992	30	PCR
Copenhagen[32]	Denmark	0	190	754	1992	26	PCR
Guanacaste[33]	Costa Rica	42	129	683	1993	38	PCR
Million Women Study[34]	UK	184	516	2,800	1999	56	None
Total		430	1,679	6,637	1993	45	
Population case-control							
Los Angeles squamous[35]	USA	200	0	198	1981	44	None
Brinton USA[36]	USA	477	291	791	1983	42	None
Male Factor[37]	Denmark	59	586	607	1985	30	None
London CIN[38]	UK	0	224	528	1985	28	None
UK cervical cancer[39]	UK	578	0	928	1986	35	Serology
Los Angeles adeno[40]	USA	141	53	373	1986	37	None
IARC[41]	Colombia (invasive)	218	0	177	1987	45	PCR
	Spain (invasive)	248	0	231	1987	53	PCR
North Thames invasive[42]	UK	119	0	242	1989	35	None
Daling Seattle[43,44]	USA	673	190	1421	1992	40	Serology
US Adeno[45]	USA	184	80	299	1993	37	PCR
Latvia[46]	Latvia	219	0	237	2000	53	PCR
Total		3,116	1,424	6,032	1986	37	
Hospital case-control							
WHO[47]	Australia	37	42	647	1981	35	None
	Nigeria	27	0	149	1981	39	None
	Philippines	154	9	733	1982	42	None
	Chile	136	154	1,051	1982	36	None
	Israel	78	32	1,929	1982	39	None
	Colombia	27	32	194	1982	37	None
	Kenya	113	3	681	1983	34	None
	Mexico	277	153	1,467	1983	39	None
	Thailand (Siriraj)	761	504	2,613	1984	41	None
	Thailand (Chulalongkom)	591	365	2,357	1984	41	None
	Thailand (Chiang Mai)	800	203	2,514	1985	46	None
Milan[48]	Invasive	781	0	878	1986	53	None
	In situ	0	270	303	1983	39	None
Brinton Latin America[6]	Colombia	212	0	407	1986	46	FISH
	Costa Rica	191	0	366	1986	44	FISH
	Mexico	155	0	291	1986	45	FISH
	Panama	192	0	307	1986	48	FISH
IARC[49–58]	Colombia (CIS)	0	234	269	1987	37	PCR
	Spain (CIS)	0	222	241	1987	35	PCR
	Paraguay	116	0	101	1990	46	PCR
	Brazil	199	0	225	1991	51	PCR
	Thailand	386	0	354	1992	50	PCR
	Mali	82	0	97	1992	45	PCR
	Philippines	387	0	386	1992	47	PCR
	Morocco	214	0	203	1992	44	PCR
	Peru	198	0	196	1997	48	PCR
	Algeria	198	0	202	1998	52	PCR
	India	205	0	213	1998	47	PCR
Bangkok[59,60]	Thailand	289	76	761	1993	41	PCR
Johannesburg[61]	South Africa	809	0	738	1997	52	Serology
Total		7,615	2,299	2,0873	1985	42	
Overall Total		11,161	5,402	3,3542	1986	41	

HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; UKCC, United Kingdom Cervical Cancer; LA, Los Angeles; IARC, International Agency for Research on Cancer; WHO, World Health Organization; RCGP, Royal College of General Practitioners; FPA, family planning association; CIS, carcinoma *in situ*.

(Los Angeles, WHO, Milan, Brinton Latin America and IARC) were counted as single studies, even when results from individual centres, or for invasive cervical carcinoma or CIN3/carcinoma *in situ,* had been published separately. Findings from the IARC studies, however, were presented separately according to the type of control women used (*i.e.*, population or hospital controls).

Four cohort studies (RCGP, Oxford FPA, Tromsø, and the Million Women Study) did not include information on lifetime number of sexual partners and age at first sexual intercourse and 1 hospital-based case-control study (Johannesburg) did not collect information on age at first sexual intercourse. As adjustment for sexual habits had a substantial influence on RRs for reproductive factors, the 4 cohort studies were not included in the computation of summary RRs in the analysis of invasive cervical carcinoma. Heterogeneity tests between study types were, therefore, possible only between population- and hospital-based case-control studies.



[1] *Conditioned on age and study or study centre.*
[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*
[3] *As in [2], and conditioned on age at first full term pregnancy.*

Figure 1 – Relative risks (RRs) of invasive cervical carcinoma and corresponding 95% floating confidence intervals (FCIs) by number of full-term pregnancies (FTPs).

A total of 11,161 women with invasive carcinoma, 5,402 women with CIN3/carcinoma *in situ* and 33,542 control women were included. Squamous cell invasive carcinoma accounted for 85% of invasive carcinoma of specified type, whereas 1,514 were invasive adenocarcinomas (15%). Specified cases of adenocarcinoma *in situ* were 301 (6% of CIN3/carcinoma *in situ*).

The median year at diagnosis by study or group of studies ranged between 1980 and 2000 and the median age at diagnosis or interview was 45 years among invasive cases (45 among squamous cell and 42 among adenocarcinomas), 35 years among CIN3/carcinoma *in situ* cases (35 among squamous cell and 36 among adenocarcinomas *in situ*) and 41 years among controls, ranging from 26 in the Copenhagen study to 56 in the Million Women Study.

Invasive cervical carcinoma

Figure 1 shows the risk of invasive cervical carcinoma by number of FTPs in all studies combined according to different adjustment models. The risk of invasive cervical carcinoma increased with number of FTPs. After adjustment for sexual factors (age at first sexual intercourse and lifetime number of sexual partners) there was still a significant risk trend (RR for $\geq$7 FTPs *vs.* nulliparous women = 2.39; 95% CI: 2.03–2.81). Among parous women, adjustment for age at first FTP attenuated the risk, but the trend remained strongly significant ($p < 0.001$). A simplified version of the fully-adjusted model was also fitted using categories 1–2, 3–4, 5–6 and $\geq$7 FTPs. The RR *vs.* 1–2 FTPs was 1.24 (95% CI: 1.12–1.37) for 3–4 FTPs, 1.44 (95% CI: 1.27–1.64) for 5–6 FTPs, and 1.76 (95% CI: 1.53–2.02) for $\geq$7 FTPs. Two hundred and forty-two invasive cervical carcinoma cases and 621 controls reported only caesarean deliveries. The RR for $\geq$2 caesarean deliveries *vs.* nulliparae was 0.82 (95% CI: 0.52–1.28, data not shown).

Figure 2 shows the risk of invasive cervical carcinoma by age at first FTP. It was possible to cover a wide range of ages for first FTP from <16 to $\geq$30, so Figure 2 presents risks in single years within this range. Women who had first FTP at older ages had similar risks to nulliparous women, and the risk increased with decreasing age at first FTP. A trend remained among parous women after adjustment for sexual factors and number of FTPs ($p < 0.001$). A simplified version of this fully-adjusted model was also fitted with cutpoints of age $\geq$25, 20–24, 17–19 and $\leq$17 years. The RR *vs.* age at first FTP $\geq$25 was 1.29 (95% CI: 1.15–1.46) for age 20–24, 1.55 (95% CI: 1.32–1.82) for age 17–19 and 1.77 (95% CI: 1.42–2.23) for age <17. Information on time since last FTP was also available for 9,704 cases of invasive cervical carcinoma and 20,517 controls. After allowance for age, study or study centre, sexual factors, number of FTPs and age at first FTP, there was no trend in risk with time since last FTP (data not shown).

Figure 3 shows the combined effect of number of FTPs and age at first FTP on cervical carcinoma risk. Among parous women, there was an increasing risk by number of FTPs within each stratum of age at first FTP, and *vice versa*. Compared to nulliparae, the RR for parity increased across strata of younger age at FTP, reaching 3.29 (95% CI: 2.58–4.21) for $\geq$7 FTPs and age at first FTP <17.

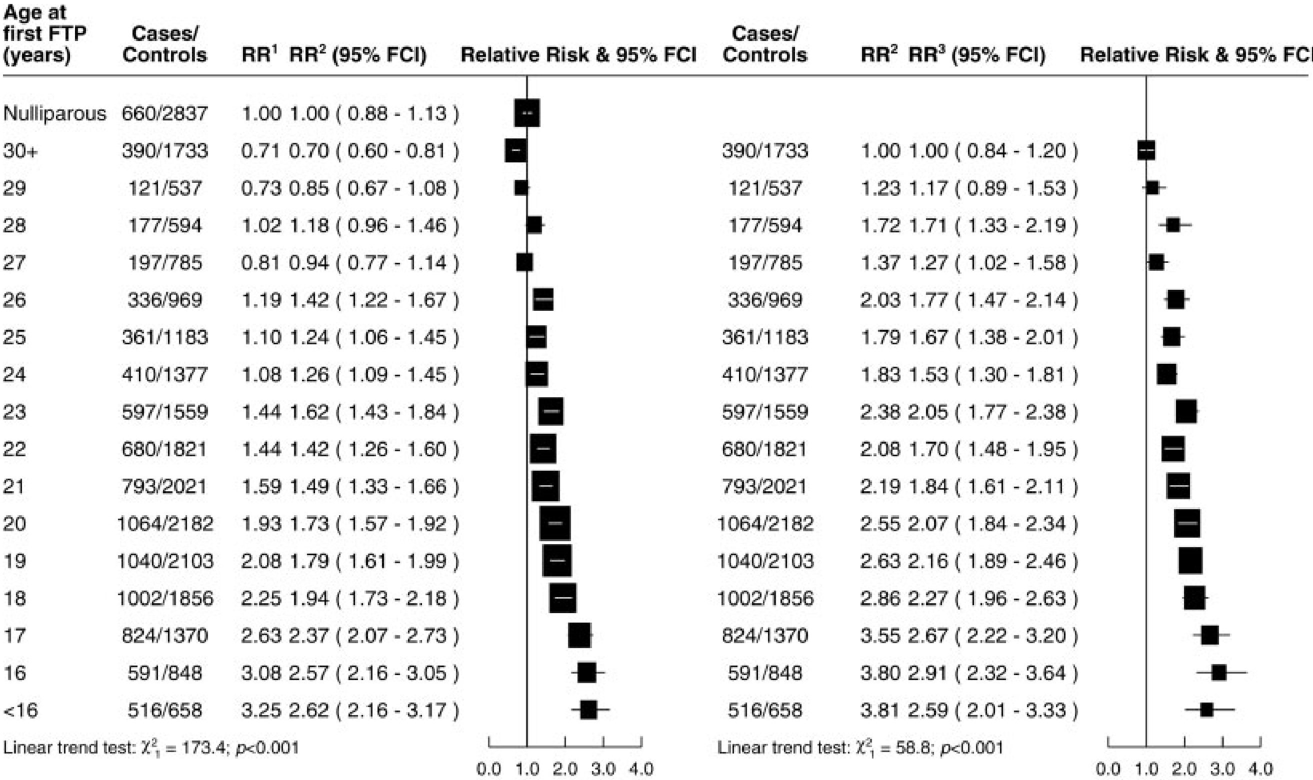
Figure 4 shows that age at first FTP was still associated with risk of invasive carcinoma within strata of women who reported the same age at first sexual intercourse. Compared to women with both age at first sexual intercourse and at first FTP $\geq$25, the RR for those who reported age at first sexual intercourse and age at first FTP <17 years was 2.59 (95% CI: 2.18–3.07).

Inter-relationship between invasive cervical carcinoma, reproductive factors and human papillomavirus

Figure 5 shows the effect of restricting the analysis to high-risk HPV-positive women. Not all studies had data on HPV infection (Table I). Therefore, to present an unbiased comparison, Figure 5 shows both HPV-restricted results and results for all women in studies that provided HPV data. The results of the 2 analyses are largely consistent for both number of FTPs and age at first FTP. Among control women, HPV infection was not associated with either age at first FTP or number of FTPs (Fig. A1).

Effect of reproductive factors by study and various characteristics

The consistency of the findings on number of FTPs and age at first FTP on invasive cervical carcinoma across studies or groups



Age at first FTP (years)	Cases/ Controls	RR[1] RR[2] (95% FCI)	Cases/ Controls	RR[2] RR[3] (95% FCI)
Nulliparous	660/2837	1.00 1.00 (0.88 - 1.13)		
30+	390/1733	0.71 0.70 (0.60 - 0.81)	390/1733	1.00 1.00 (0.84 - 1.20)
29	121/537	0.73 0.85 (0.67 - 1.08)	121/537	1.23 1.17 (0.89 - 1.53)
28	177/594	1.02 1.18 (0.96 - 1.46)	177/594	1.72 1.71 (1.33 - 2.19)
27	197/785	0.81 0.94 (0.77 - 1.14)	197/785	1.37 1.27 (1.02 - 1.58)
26	336/969	1.19 1.42 (1.22 - 1.67)	336/969	2.03 1.77 (1.47 - 2.14)
25	361/1183	1.10 1.24 (1.06 - 1.45)	361/1183	1.79 1.67 (1.38 - 2.01)
24	410/1377	1.08 1.26 (1.09 - 1.45)	410/1377	1.83 1.53 (1.30 - 1.81)
23	597/1559	1.44 1.62 (1.43 - 1.84)	597/1559	2.38 2.05 (1.77 - 2.38)
22	680/1821	1.44 1.42 (1.26 - 1.60)	680/1821	2.08 1.70 (1.48 - 1.95)
21	793/2021	1.59 1.49 (1.33 - 1.66)	793/2021	2.19 1.84 (1.61 - 2.11)
20	1064/2182	1.93 1.73 (1.57 - 1.92)	1064/2182	2.55 2.07 (1.84 - 2.34)
19	1040/2103	2.08 1.79 (1.61 - 1.99)	1040/2103	2.63 2.16 (1.89 - 2.46)
18	1002/1856	2.25 1.94 (1.73 - 2.18)	1002/1856	2.86 2.27 (1.96 - 2.63)
17	824/1370	2.63 2.37 (2.07 - 2.73)	824/1370	3.55 2.67 (2.22 - 3.20)
16	591/848	3.08 2.57 (2.16 - 3.05)	591/848	3.80 2.91 (2.32 - 3.64)
<16	516/658	3.25 2.62 (2.16 - 3.17)	516/658	3.81 2.59 (2.01 - 3.33)

Linear trend test: $\chi^2_1 = 173.4$; $p<0.001$ Linear trend test: $\chi^2_1 = 58.8$; $p<0.001$

[1] *Conditioned on age and study or study centre.*
[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*
[3] *As in [2], and conditioned on number of full term pregnancies.*

FIGURE 2 – Relative risks (RRs) of invasive cervical carcinoma and corresponding 95% floating confidence intervals (FCIs) by age at first full-term pregnancy (FTP).

of studies is shown in Figures A2 and A3. The overall mean number of FTPs was 4.1 for cases and 3.1 for controls (Fig. A2). The study- and age-adjusted RR for 1 additional FTP was 1.13 (95% CI: 1.11–1.14). Adjustment for sexual factors was possible in 16 studies, including 9,812 women with invasive carcinoma and 24,716 controls. The summary RR in this restricted series was 1.10 (95% CI: 1.08–1.12). The estimates were significantly heterogeneous between studies, but not between groups of population-based studies and hospital-based case-control studies (RR = 1.12; 95% CI: 1.08–1.16 and 1.10; 95% CI: 1.08–1.12, respectively). The RR estimates were not materially modified by adjustment for number of Pap smears (RR = 1.11), education (RR = 1.09), cigarette smoking (RR = 1.13), hormonal contraceptive use (RR = 1.12) or condom use (RR = 1.12).

The mean age at first FTP was 20.9 years among cervical cancer cases (range of study-specific means: 19.4–24.3) and 22.4 among controls (range: 19.9–25.3, Fig. A3). The overall study- and age-adjusted RR for 1-year decrease in age at first FTP was 1.09 (95% CI: 1.09–1.10). Adjustment for sexual factors reduced the number of subjects to 9,099 invasive cervical carcinoma cases and 21,596 controls. In this restricted subset, the overall RR was 1.07 (95% CI: 1.06–1.09). Results were homogeneous between population- and hospital-based case-control studies (RR for a 1-year decrease in age at first FTP = 1.08; 95% CI: 1.06–1.10 and 1.07; 95% CI: 1.06–1.09, respectively). These risk estimates were not materially modified by adjustment for number of Pap smears (RR = 1.09), education (RR = 1.08), cigarette smoking (RR = 1.09), hormonal contraceptive (RR = 1.09) and condom use (RR = 1.09).

The relation between number of FTPs (Fig. A4), age at first FTP (Fig. A5), and invasive cervical carcinoma was also analysed separately in women with different characteristics. Similar risk patterns were found for women with different age, type of country, education level, cigarette smoking status, history of Pap smear, number of lifetime sexual partners and use of condoms and of hormonal contraceptives.

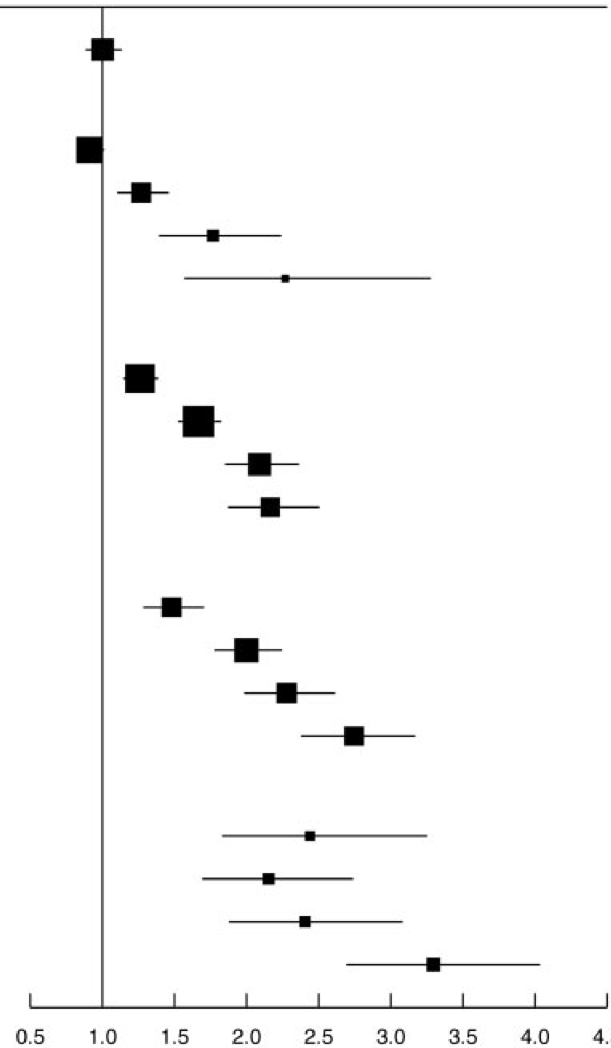
The effect of number of FTPs and age at first FTP was also evaluated separately for the 2 major histological groups (data not shown). After adjustment for sexual factors and age at first FTP, the RR for $\geq$7 FTPs *vs.* 1–2 was 1.78 (95% CI: 1.53–2.08) for squamous cell carcinoma and 1.34 (95% CI: 0.95–1.90) for adenocarcinoma (including adenosquamous carcinoma). Similarly, the RR among women $<$17 years of age at first FTP *vs.* $>$25 years was 1.77 (95% CI: 1.38–2.29) for squamous cell carcinoma and 1.35 (95% CI: 0.77–2.38) for adenocarcinoma (including adenosquamous carcinoma) after adjustment for sexual factors and number of FTPs.

Cervical intraepithelial neoplasia grade 3/carcinoma in situ

Figures 6 and 7 show the risk of CIN3/carcinoma *in situ* by number of FTPs and age at first FTP, respectively. These figures are equivalent to Figures 1 and 2 for invasive cervical carcinoma, but use broader categories for the 2 risk factors. The risk of CIN3/carcinoma *in situ* increased with number of FTPs (RR for $\geq$7 *vs.* nulliparous women after adjustment for lifetime number of sexual partners and age at first sexual intercourse = 1.60; 95% CI: 1.24–2.08). There was no significant trend in risk with number of FTPs, among parous women, after controlling for sexual factors and age at first FTP (p = 0.27). Conversely, the risk associated with age at first FTP was unaffected by controlling for the number of FTPs. A

Number of FTPs	Cases/ Controls	RR[1]	RR[2] (95% FCI)
Nulliparous	660/2837	1.00	1.00 (0.88 - 1.13)
Age at first FTP: 25+ years			
1-2	903/3705	0.81	0.91 (0.82 - 1.01)
3-4	448/1554	1.13	1.27 (1.10 - 1.46)
5-6	156/397	1.50	1.77 (1.39 - 2.24)
7+	75/145	2.33	2.27 (1.57 - 3.28)
Age at first FTP: 20-24 years			
1-2	1097/3422	1.27	1.26 (1.14 - 1.39)
3-4	1201/3064	1.65	1.67 (1.52 - 1.82)
5-6	681/1402	2.14	2.09 (1.85 - 2.36)
7+	565/1072	2.26	2.16 (1.87 - 2.50)
Age at first FTP: 17-19 years			
1-2	581/1405	1.97	1.48 (1.28 - 1.70)
3-4	877/1666	2.36	2.00 (1.78 - 2.24)
5-6	626/1077	2.67	2.28 (1.98 - 2.61)
7+	782/1181	2.92	2.74 (2.38 - 3.17)
Age at first FTP: <17 years			
1-2	162/273	3.42	2.44 (1.83 - 3.25)
3-4	237/381	3.07	2.15 (1.69 - 2.74)
5-6	237/327	3.37	2.40 (1.88 - 3.08)
7+	471/525	3.76	3.29 (2.69 - 4.03)

Relative risks & 95% FCI



[1] *Conditioned on age and study or study centre.*

[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*

FIGURE 3 – Relative risks (RRs) of invasive cervical carcinoma and corresponding 95% floating confidence intervals (FCIs) by number of full-term pregnancies (FTPs) stratified by age at first FTP.

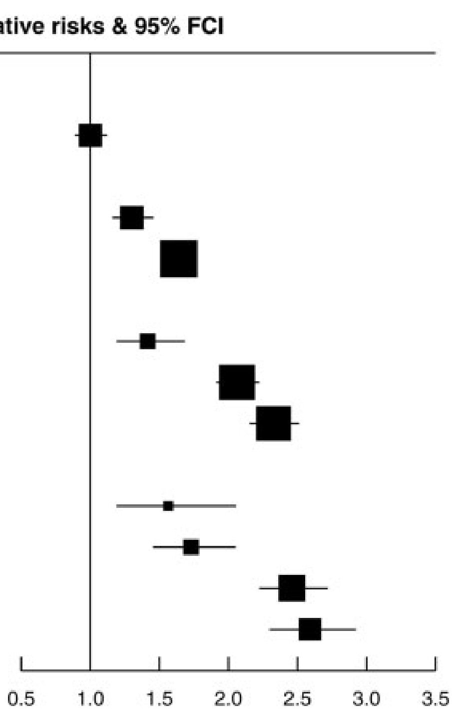
significant risk trend was seen among parous women ($p < 0.001$), with a RR of 1.78 (95% CI: 1.26–2.51) for first FTP at age <17 years compared with $\geq$25 years. The consistency of the findings on number of FTPs and age at first FTP across studies or groups of studies on cervical CIN3/carcinoma *in situ* is shown in Figures A6 and A7. The mean number of FTPs was 2.3 among cases and 2.8 among control women (Fig. A6). The overall RR for a 1-FTP increase was 1.07, and adjustment for sexual factors reduced the pooled overall RR to 1.06 (95% CI: 1.03–1.09). Significant heterogeneity emerged between individual studies and types of study design. The sexual habit-adjusted RR was 1.10 for cohort studies, 1.11 for case-control studies with population controls and 1.04 for case-control studies with hospital controls.

The mean age at first FTP was 22 years among CIN3/carcinoma *in situ* cases and 22.5 among controls (Fig. A7). The overall RR for 1-year decrease in age at first FTP was 1.05 before, and 1.04 (95% CI: 1.03–1.06) after adjustment for sexual variables. Significant heterogeneity emerged between studies, but RRs did not differ significantly between study designs (1.03 for cohort studies, 1.06 for population-based case-control studies and 1.04 for hospital-based case-control studies).

Discussion

The present collaborative reanalysis provides evidence, and more accurate quantification than previously available, on the direct relationship between the risk of cervical cancer and parity, and the inverse one with age at first FTP. Despite the strong correlation between parity and age at first FTP, the effects of these 2 variables were independent, since reciprocal allowance only marginally reduced the association with invasive cervical carcinoma. Furthermore, the association with reproductive factors remained after adjusting for major indicators of sexual habits (lifetime number of sexual partners and age at first sexual intercourse), or history of Pap smear, and was also evident, and of similar magnitude, when analysis was restricted to HPV-positive women. Findings on

Age at 1st FTP(years)	Cases/ Controls	RR[1]	RR[2] (95% FCI)
Age at first intercourse: 25+			
25+	577/2625	1.00	1.00 (0.89 - 1.12)
Age at first intercourse: 20-24			
25+	587/2090	1.33	1.30 (1.16 - 1.46)
20-24	1637/4730	1.90	1.64 (1.53 - 1.76)
Age at first intercourse: 17-19			
25+	296/789	2.00	1.42 (1.19 - 1.68)
20-24	1513/3484	2.56	2.06 (1.91 - 2.23)
17-19	1676/3300	3.05	2.33 (2.15 - 2.51)
Age at first intercourse: <17			
25+	122/297	2.10	1.57 (1.19 - 2.06)
20-24	394/746	3.02	1.73 (1.45 - 2.05)
17-19	1190/2029	3.76	2.46 (2.22 - 2.72)
<17	1107/1506	4.51	2.59 (2.30 - 2.92)



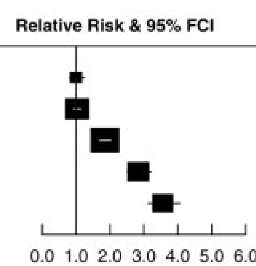
[1] *Conditioned on age and study or study centre.*

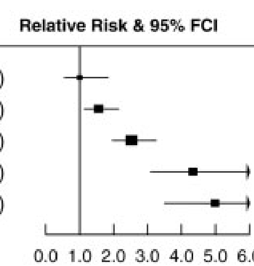
[2] *As in [1], and conditioned on lifetime number of sexual partners and number of full term pregnancies.*

FIGURE 4 – Relative risks (RRs) of invasive cervical carcinoma and corresponding 95% floating confidence intervals (FCIs) by age at first full-term pregnancy (FTP) stratified by age at first intercourse.

Cervical cancer in studies with HR HPV DNA information / **Cervical cancer among HR HPV DNA positive women**

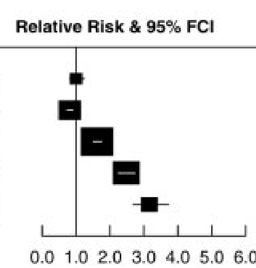
Number of FTPs	Cases/ Controls	RR[1] (95% FCI)	Cases/ Controls	RR[1] (95% FCI)
Nulliparous	137/472	1.00 (0.79 - 1.26)	71/111	1.00 (0.54 - 1.85)
1-2	668/2045	1.04 (0.93 - 1.17)	448/459	1.56 (1.13 - 2.17)
3-4	854/1553	1.86 (1.69 - 2.04)	649/328	2.53 (1.95 - 3.27)
5-6	648/764	2.84 (2.49 - 3.22)	494/149	4.34 (3.08 - 6.11)
7+	867/953	3.56 (3.11 - 4.07)	706/195	4.99 (3.49 - 7.13)

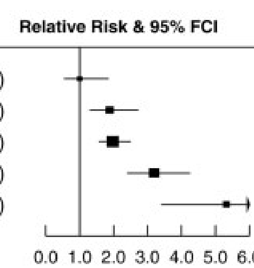




Linear trend test: χ^2_1 = 195.9; p<0.001 | Linear trend test: χ^2_1 = 30.69; p<0.001

Age at 1st FTP(years)	Cases/ Controls	RR[1] (95% FCI)	Cases/ Controls	RR[1] (95% FCI)
Nulliparous	137/472	1.00 (0.79 - 1.26)	71/111	1.00 (0.54 - 1.86)
25+	446/1125	0.82 (0.72 - 0.93)	314/111	1.88 (1.29 - 2.73)
20-24	1135/1797	1.62 (1.49 - 1.77)	846/314	1.98 (1.56 - 2.51)
17-19	963/1281	2.48 (2.23 - 2.75)	736/327	3.20 (2.40 - 4.25)
<17	469/560	3.16 (2.67 - 3.74)	381/153	5.32 (3.40 - 8.34)



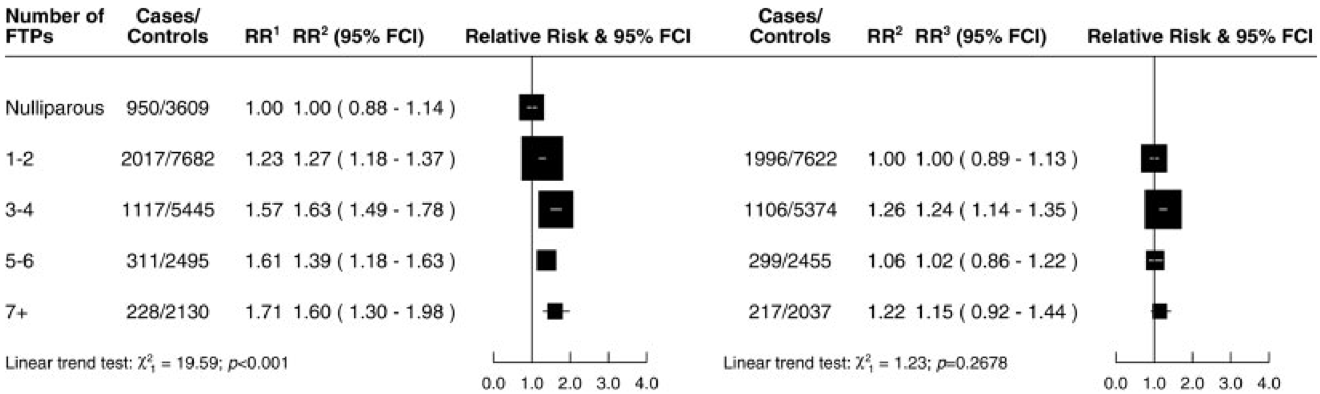


Linear trend test: χ^2_1 = 208.9; p<0.001 | Linear trend test: χ^2_1 = 23.66; p<0.001

[1] *Conditioned on age and study or study centre.*

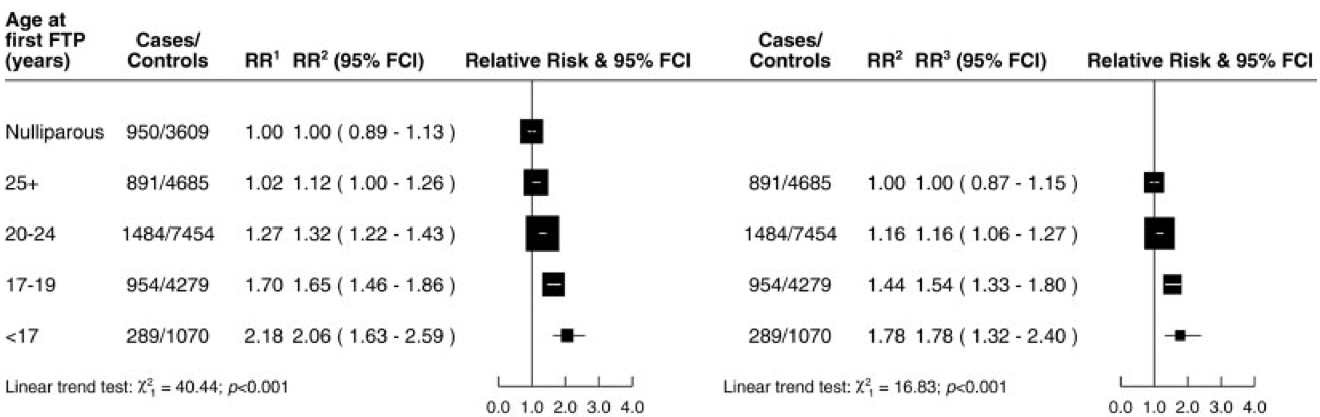
RR, relative risk; FCI, floating confidence interval.

FIGURE 5 – Effect of restriction to women positive for DNA of high-risk (HR) human papillomavirus (HPV) types on risk of invasive cervical carcinoma.



[1] *Conditioned on age and study or study centre.*
[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*
[3] *As in [2], and conditioned on age at first full term pregnancy.*

Figure 6 – Relative risks (RRs) of CIN3/carcinoma *in situ* and corresponding 95% floating confidence intervals (FCIs) by number of full-term pregnancies (FTPs).



[1] *Conditioned on age and study or study centre.*
[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*
[3] *As in [2], and conditioned on number of full term pregnancies.*

Figure 7 – Relative risks (RRs) of CIN3/carcinoma *in situ* and corresponding 95% floating confidence intervals (FCIs) by age at first full-term pregnancy (FTP).

cervical cancer and reproductive factors have been published from 6 studies that could not be included. The results of these studies were consistent with our present results.[16,17,19,21–24]

The difficulty of disentangling the effect of reproductive variables from sexual behaviour and HPV infection cannot, however, be overstated. If the number of sexual partners is inaccurately reported, or information on some potentially relevant aspects of sexual behaviour (*e.g.*, husband's sexual behaviour in our present reanalysis) is not available, a residual confounding effect cannot be completely ruled out. HPV infection, conversely, may be considered an extreme example of effect modification (*i.e.*, reproductive factors would be irrelevant in the absence of high-risk HPV infection). The lack of association between reproductive factors and high-risk HPV positivity among controls and the confirmation of the direct associations with reproductive factors among high-risk HPV-positive women provides, however, evidence that multiparity and early childbearing contribute, along with high-risk HPV infection, to the risk of developing invasive cervical carcinoma. Such evidence is, however, less than perfect, on account of the small number of high-risk HPV-positive control women, even in our large pooled analysis, and the difficulty in interpreting HPV negativity among cervical cancer cases and HPV positivity at a moment in time among control women.

The presence of HPV DNA in cervical cancer specimens is assumed to be the marker of a long-standing infection, given the long latency of HPV-induced carcinogenesis. Conversely, HPV-positive control women may suffer from recent infection and HPV-negative control women may well have been infected in the past and cleared the infection spontaneously.

Among different study designs, cohort studies showed the smallest associations between invasive cervical carcinoma and parity, but included less than 6% of all cases, and their 95% CIs largely overlapped with those from case-control studies. The results for parity were similar for hospital- and population-based case-control studies. Likewise, the results for age at first FTP were similar across various populations and study designs. The consistency of the association with the number of FTPs strongly supports the existence of a real association, although studies conducted in developed countries included too few women with $\geq$3 FTPs to provide reliable estimates of risk for women with very high parity.

The same line of reasoning applies to early first FTP, which, in the extreme categories, essentially included data from studies conducted in developing countries. The association of risk of invasive cervical carcinoma with reproductive factors was similar across strata of geographic area, education, cigarette smoking, history of Pap smear and use of contraceptive methods.

The association of risk of CIN3/carcinoma *in situ* with age at first FTP was similar in magnitude to the risk of invasive carcinoma. For number of FTPs, the results were somewhat different for invasive and *in situ* carcinoma. Among parous women, there was no clear evidence that the risk of CIN3/carcinoma *in situ* increased with increasing number of FTPs. Therefore it is possible that there is no association with number of FTPs, or that the association is weaker than for invasive carcinoma.

The association between parity and invasive cervical carcinoma may have a number of different explanations. High concentrations of oestrogen and progesterone during pregnancy and delivery-related cervical traumas cause the eversion of the columnar epithelium onto the ectocervix (ectopy), which in turn favours the exposure of the squamo-columnal junction to HPV infection. Interestingly, the few women who reported caesarean, but not vaginal deliveries, did not show increased risk compared to nulliparae. The hormonal profile of pregnancy could favour, or accelerate, cervical carcinogenesis, with a mechanism similar to that put forward to explain the increased risk of cervical neoplasia in long-term oral contraceptive users,[36,62] *e.g.*, glucocorticoid-dependent oncogenic transformation by HPV.[63] Immunodepression caused by pregnancy may also favour the infection, or the oncogenic potential of HPV.[64]

The public health implications of our findings on reproductive factors and cervical cancer are relatively limited for areas of the world where parity is 1 or 2 children per woman, including most developed countries, but also, at the present time, some Asian countries (*e.g.*, China). The results are of major relevance, however, for world areas where multiparity is frequent and cervical cancer is common, such as Africa or Latin America.[9,65] To illustrate the possible contribution of reproductive factors in developing countries, we estimated what the absolute risk of cervical cancer would have been in our present dataset if parity and age at first FTP in these countries had been the same as in developed countries. The cumulative risk of developing cervical cancer by age 65 in developing countries was on average 2.2% in the late 1980s.[66] If mean parity in developing countries had been 2.5 FTPs (as in developed countries) instead of 3.8, the cumulative risk would have been 1.8%. If mean age at first FTP had been 23.6 instead of 21.7, the absolute risk would have further decreased to 1.5%, *i.e.*, a total reduction of around 30% in absolute risk, in the absence of changes in HPV prevalence.

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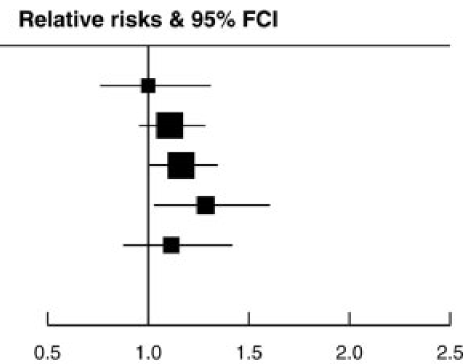
Appendix

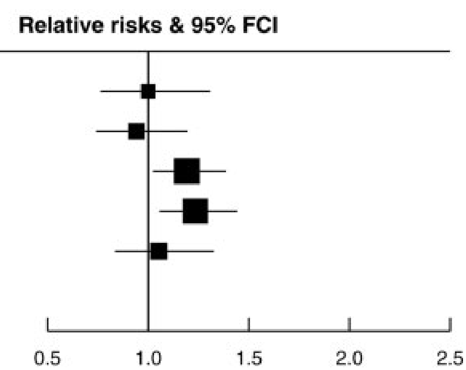
Number of FTPs	Positive/ Negative	RR[1] (95% FCI)
Nulliparous	111/303	1.00 (0.76 - 1.31)
1-2	459/1333	1.11 (0.95 - 1.28)
3-4	328/1018	1.16 (1.01 - 1.35)
5-6	149/506	1.28 (1.03 - 1.60)
7+	195/630	1.12 (0.88 - 1.42)

Linear trend test: $\chi^2_1 = 0.59$; p=0.442



Age at 1st FTP(years)	Positive/ Negative	RR[1] (95% FCI)
Nulliparous	111/303	1.00 (0.76 - 1.31)
25+	111/813	0.94 (0.74 - 1.20)
20-24	314/1224	1.19 (1.02 - 1.39)
17-19	327/800	1.23 (1.06 - 1.44)
<17	153/325	1.05 (0.84 - 1.32)

Linear trend test: $\chi^2_1 = 1.28$; p=0.259

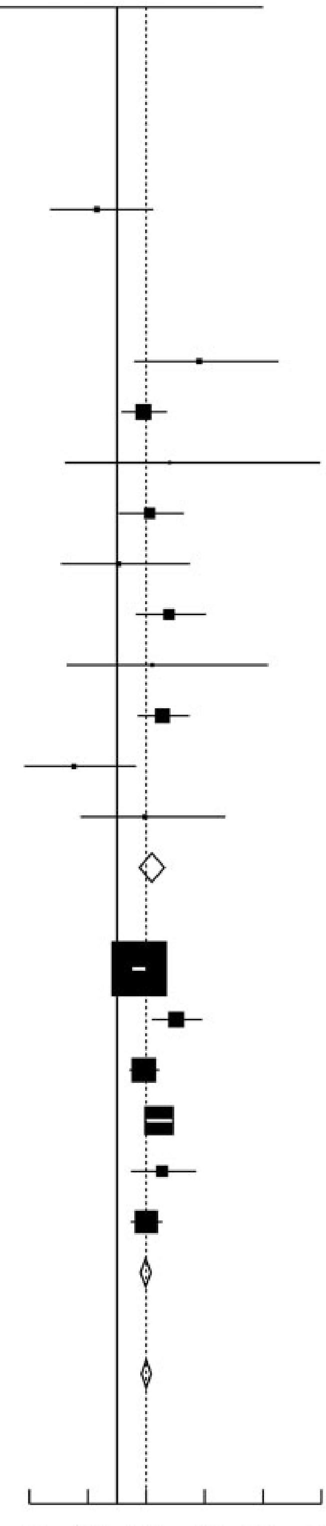


[1] *Conditioned on age and study or study centre.*

FIGURE A1 – Relative risks (RRs) and corresponding 95% floating confidence intervals (FCIs) of infection with high-risk HPV types among control women by number of full-term pregnancies (FTPs) and age at first FTP.

Centre	Cases/ Controls	Mean number of FTPs	RR[1]	RR[2] (95% CI)
Cohort studies				
RCGP[3]	162/609	2.8 / 2.4	1.27	-
Oxford FPA[3]	42/154	2.5 / 2.3	1.04	-
Guanacaste	39/683	5.8 / 4.4	1.03	0.93 (0.77 - 1.12)
Million Women Study[3]	184/2794	2.2 / 2.1	1.04	-
Case-control studies - population controls				
Los Angeles squamous	198/195	3.8 / 3.1	1.15	1.28 (1.06 - 1.55)
Brinton USA	470/785	3.4 / 2.7	1.11	1.09 (1.01 - 1.17)
Male Factor	57/590	1.5 / 1.0	1.33	1.18 (0.82 - 1.70)
UK cervical cancer	576/926	2.1 / 1.9	1.19	1.11 (1.01 - 1.23)
Los Angeles adeno	141/373	1.8 / 1.7	1.05	1.01 (0.81 - 1.25)
IARC Studies	456/403	4.3 / 3.5	1.12	1.18 (1.06 - 1.30)
North Thames invasive	118/242	1.6 / 1.5	1.07	1.12 (0.83 - 1.52)
Daling Seattle	671/1414	2.2 / 1.9	1.13	1.16 (1.07 - 1.25)
US Adeno	155/262	2.0 / 1.7	1.03	0.85 (0.68 - 1.07)
Latvia	212/235	2.1 / 1.7	1.19	1.10 (0.88 - 1.37)
All population cc	3054/5425	2.7 / 2.0	1.12	1.12 (1.08 - 1.16)
Case-control studies - hospital controls				
WHO Studies	2975/13734	4.5 / 3.5	1.11	1.08 (1.05 - 1.10)
Milan	764/844	2.5 / 1.9	1.21	1.20 (1.12 - 1.29)
Brinton Latin America	731/1336	6.0 / 4.9	1.12	1.09 (1.04 - 1.14)
IARC Studies	1960/1933	5.7 / 4.5	1.16	1.14 (1.10 - 1.19)
Bangkok	289/761	3.7 / 2.8	1.20	1.15 (1.05 - 1.27)
Johannesburg[4]	794/730	4.2 / 3.6	1.09	1.10 (1.05 - 1.16)
All hospital cc	7513/19338	4.7 / 3.6	1.13	1.10 (1.08 - 1.12)
All studies	10994/29003	4.1 / 3.1	1.13	1.10 (1.08 - 1.12)

Relative risks & 95% CI



Heterogeneity test between studies $\chi^2_{15} = 32.84$; $p = 0.005$
Heterogeneity test between study designs $\chi^2_{1} = 1.34$; $p = 0.247$

[1] Conditioned on age and study or study centre.

[2] As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.

[3] RR[2] not calculated for lack of information on sexual variables.

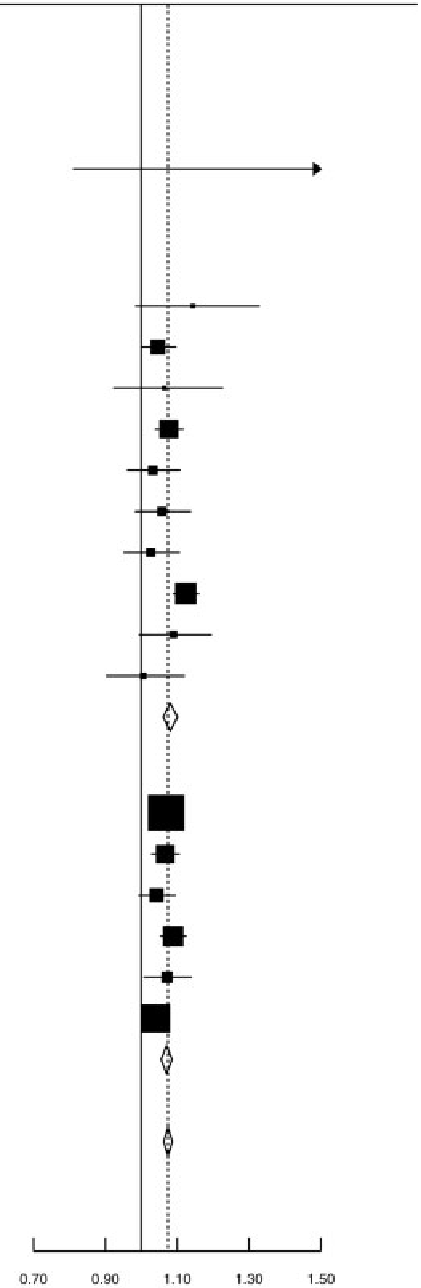
[4] RR[2] not conditioned on age at first sexual intercourse and not considered in the heterogeneity test.

FIGURE A2 – Relative risks (RRs) of invasive cervical carcinoma and corresponding 95% confidence intervals (CIs) increase of 1 full-term pregnancy (FTP) and by study and study design.

Centre	Cases/ Controls	Mean age at 1st FTP	RR[1]	RR[2] (95% CI)
Cohort studies				
RCGP[3]	6/53	24.3/25.3	1.04	-
Oxford FPA[3]	39/135	22.1/24.0	1.14	-
Guanacaste	23/446	19.4/19.9	1.05	1.35 (0.81 - 2.25)
Million Women Study[3]	158/2442	22.5/24.1	1.11	-
Case-control studies - population controls				
Los Angeles squamous	166/168	20.2/22.3	1.14	1.14 (0.98 - 1.33)
Brinton USA	415/661	20.5/22.2	1.08	1.05 (1.00 - 1.10)
Male Factor	38/349	22.6/23.4	1.08	1.06 (0.92 - 1.23)
UK cervical cancer	497/777	21.3/23.2	1.11	1.08 (1.04 - 1.12)
Los Angeles adeno	102/280	21.6/23.5	1.09	1.03 (0.96 - 1.11)
IARC Studies	430/379	21.5/23.7	1.13	1.06 (0.98 - 1.14)
North Thames invasive	85/186	22.4/24.6	1.09	1.03 (0.95 - 1.11)
Daling Seattle	543/1080	21.6/24.2	1.13	1.12 (1.09 - 1.16)
US Adeno	114/197	21.9/24.1	1.12	1.09 (0.99 - 1.20)
Latvia	195/202	22.1/22.6	1.06	1.01 (0.90 - 1.12)
All population cc	2585/4279	21.4/23.4	1.11	1.08 (1.06 - 1.10)
Case-control studies - hospital controls				
WHO Mexico	2889/12344	20.7/21.9	1.09	1.07 (1.05 - 1.09)
Milan	694/720	23.7/25.3	1.07	1.07 (1.03 - 1.11)
Brinton Colombia	712/1265	19.4/20.9	1.09	1.04 (0.99 - 1.10)
IARC Studies	1915/1836	19.7/21.5	1.11	1.09 (1.05 - 1.13)
Bangkok	281/706	21.5/23.2	1.10	1.07 (1.01 - 1.14)
Johannesburg[4]	772/651	20.9/21.7	1.04	1.04 (1.02 - 1.07)
All hospital cc	7263/17522	20.6/22.0	1.09	1.07 (1.06 - 1.09)
All studies	10074/24877	20.9/22.4	1.09	1.07 (1.06 - 1.09)

Heterogeneity test between studies $\chi^2_{15} = 18.31$; $p = 0.247$
Heterogeneity test between study designs $\chi^2_{1} = 0.38$; $p = 0.537$

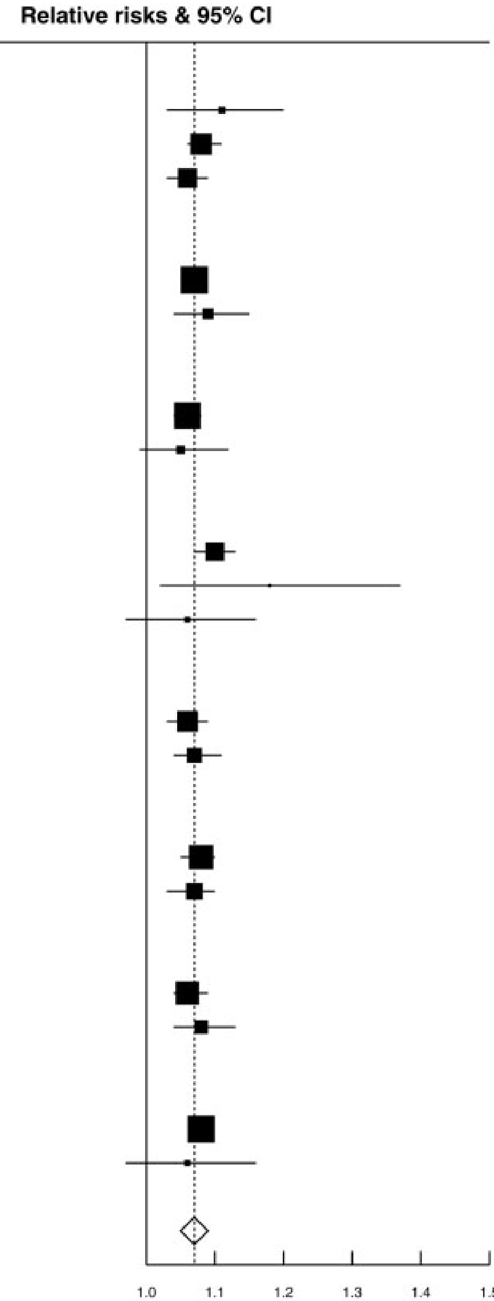
Relative risks & 95% CI



[1] *Conditioned on age and study or study centre.*
[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*
[3] *RR[2] not calculated for lack of information on sexual variables.*
[4] *RR[2] not conditioned on age at first sexual intercourse and not considered in the heterogeneity test.*

FIGURE A3 – Relative risks (RRs) of invasive cervical carcinoma and corresponding 95% confidence intervals (CIs) by 1-year decrease in age at first full-term pregnancy (FTP) and by study and study design.

Subgroup	Cases	Controls	RR[1] (95% CI)
Age			
<35	1479	5317	1.11 (1.03 - 1.20)
35-49	4477	10785	1.08 (1.06 - 1.11)
50+	3143	5494	1.06 (1.03 - 1.09)
Test for heterogeneity $\chi^2_2 = 2.81$; $p = 0.245$			
Location			
developing countries	5931	14953	1.07 (1.05 - 1.09)
developed countries	3168	6643	1.09 (1.04 - 1.15)
Test for heterogeneity $\chi^2_1 = 0.66$; $p = 0.416$			
Education			
<10	5883	13528	1.06 (1.04 - 1.08)
10+	2472	7314	1.05 (0.99 - 1.12)
Test for heterogeneity $\chi^2_1 = 0.13$; $p = 0.720$			
Cigarette smoking			
Never	5110	10056	1.10 (1.07 - 1.13)
Past	858	1386	1.18 (1.02 - 1.37)
Current	1476	2063	1.06 (0.97 - 1.16)
Test for heterogeneity $\chi^2_2 = 1.62$; $p = 0.445$			
Pap smear			
0	4866	9779	1.06 (1.03 - 1.09)
1+	3861	10890	1.07 (1.04 - 1.11)
Test for heterogeneity $\chi^2_1 = 0.34$; $p = 0.560$			
Lifetime number of sexual partners			
Monogamous	4972	15101	1.08 (1.05 - 1.10)
2+	4127	6495	1.07 (1.03 - 1.10)
Test for heterogeneity $\chi^2_1 = 0.33$; $p = 0.565$			
Hormonal contraceptive use			
Never	5195	11778	1.06 (1.04 - 1.09)
Ever	3904	9818	1.08 (1.04 - 1.13)
Test for heterogeneity $\chi^2_1 = 0.64$; $p = 0.422$			
Condom use			
no	7393	16783	1.08 (1.06 - 1.10)
yes	1569	4160	1.06 (0.97 - 1.16)
Test for heterogeneity $\chi^2_1 = 0.14$; $p = 0.707$			
All women	9099	21596	1.07 (1.05 - 1.09)

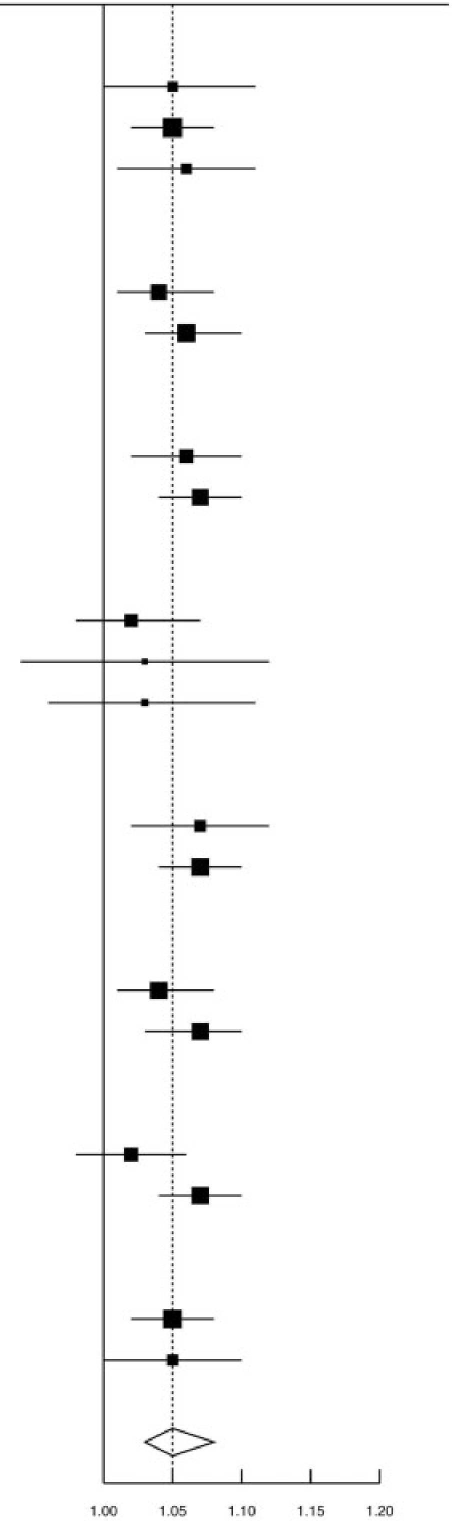


[1] *Conditioned on age at diagnosis, study or study centre, age at first sexual intercourse, lifetime number of sexual partners when appropriate and age at first full term pregnancy.*

FIGURE A4 – Relative risks (RRs) of invasive cervical carcinoma and corresponding 95% confidence intervals (CIs) by increase in 1 full-term pregnancy and stratified by various characteristics.

Subgroup	Cases	Controls	RR[1] (95% CI)
Age			
<35	1479	5317	1.05 (1.00 - 1.11)
35-49	4477	10785	1.05 (1.02 - 1.08)
50+	3143	5494	1.06 (1.01 - 1.11)
Test for heterogeneity $\chi^2_2 = 2.21$; p 0.331			
Location			
developing countries	5931	14953	1.04 (1.01 - 1.08)
developed countries	3168	6643	1.06 (1.03 - 1.10)
Test for heterogeneity $\chi^2_1 = 0.47$; $p = 0.492$			
Education			
<10	5883	13528	1.06 (1.02 - 1.10)
10+	2472	7314	1.07 (1.04 - 1.10)
Test for heterogeneity $\chi^2_1 = 0.92$; $p = 0.338$			
Cigarette smoking			
Never	5110	10056	1.02 (0.98 - 1.07)
Past	858	1386	1.03 (0.94 - 1.12)
Current	1476	2063	1.03 (0.96 - 1.11)
Test for heterogeneity $\chi^2_2 = 1.84$; $p = 0.398$			
Pap smear			
0	4866	9779	1.07 (1.02 - 1.12)
1+	3861	10890	1.07 (1.04 - 1.10)
Test for heterogeneity $\chi^2_1 = 0.03$; $p = 0.861$			
Lifetime number of sexual partners			
Monogamous	4972	15101	1.04 (1.01 - 1.08)
2+	4127	6495	1.07 (1.03 - 1.10)
Test for heterogeneity $\chi^2_1 = 0.01$; $p = 0.903$			
Hormonal contraceptive use			
Never	5195	11778	1.02 (0.98 - 1.06)
Ever	3904	9818	1.07 (1.04 - 1.10)
Test for heterogeneity $\chi^2_1 = 2.98$; $p = 0.085$			
Condom use			
no	7393	16783	1.05 (1.02 - 1.08)
yes	1569	4160	1.05 (1.00 - 1.10)
Test for heterogeneity $\chi^2_1 = 0.00$; $p = 0.987$			
All women	9099	21596	1.05 (1.03 - 1.08)

Relative risks & 95% CI



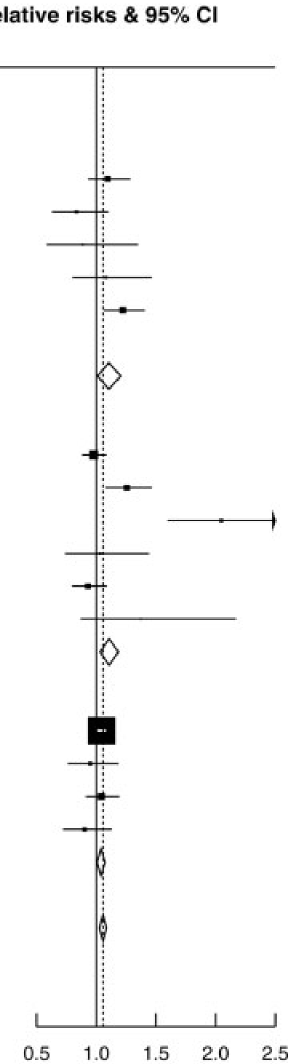
[1] Conditioned on age at diagnosis, study or study centre, age at first sexual intercourse, lifetime number of sexual partners when appropriate and number of full term pregnancies.

FIGURE A5 – Relative risks (RRs) of invasive cervical carcinoma and corresponding 95% confidence intervals (CIs) by 1-year decrease in age at first full-term pregnancy and stratified by various characteristics.

Centre	Cases/ Controls	Mean number of FTPs	RR[1]	RR[2] (95% CI)
Cohort studies				
Tromsø[3]	133/475	1.9/2.0	1.03	-
Sweden	377/377	1.8/1.8	1.02	1.09 (0.93 - 1.29)
Manchester	199/179	1.5/1.3	1.05	0.83 (0.63 - 1.10)
Portland Kaiser	62/260	1.0/1.4	0.75	0.89 (0.58 - 1.35)
Copenhagen	190/753	0.3/0.2	1.08	1.08 (0.80 - 1.46)
Guanacaste	129/683	4.5/4.4	1.10	1.22 (1.06 - 1.41)
Million Women Study[3]	514/2794	2.3/2.1	1.14	-
All cohorts	957/2252	1.9/2.0	1.08	1.10 (1.01 - 1.21)
Case-control studies - population controls				
Brinton USA	290/785	2.1/2.7	0.96	0.98 (0.88 - 1.09)
Male Factor	563/590	1.1/1.0	1.18	1.26 (1.08 - 1.47)
London CIN	224/527	0.9/0.4	2.02	2.05 (1.60 - 2.63)
Los Angeles adeno	53/373	1.7/1.7	1.02	1.03 (0.74 - 1.44)
Daling Seattle	190/1414	1.4/1.9	0.91	0.93 (0.80 - 1.09)
US Adeno	65/262	1.3/1.7	0.90	1.37 (0.87 - 2.17)
All population cc	1385/3951	1.4/1.7	1.04	1.11 (1.03 - 1.19)
Case-control studies - hospital controls				
WHO studies	1487/13586	3.4/3.5	1.07	1.05 (1.01 - 1.08)
Milan in situ	267/302	1.8/1.8	0.90	0.95 (0.76 - 1.18)
IARC studies	451/509	3.1/2.8	1.14	1.04 (0.91 - 1.19)
Bangkok	76/761	2.6/2.8	1.12	0.90 (0.72 - 1.13)
All hospital cc	2281/15158	3.1/3.4	1.07	1.04 (1.01 - 1.07)
All studies	4623/21361	2.3/2.8	1.07	1.06 (1.03 - 1.09)

Heterogeneity test between studies $\chi^2_{14} = 58.40$; $p<0.0001$

Heterogeneity test between study designs $\chi^2_{2} = 8.39$; $p=0.015$



[1] *Conditioned on age at diagnosis, study or study centre.*

[2] *As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.*

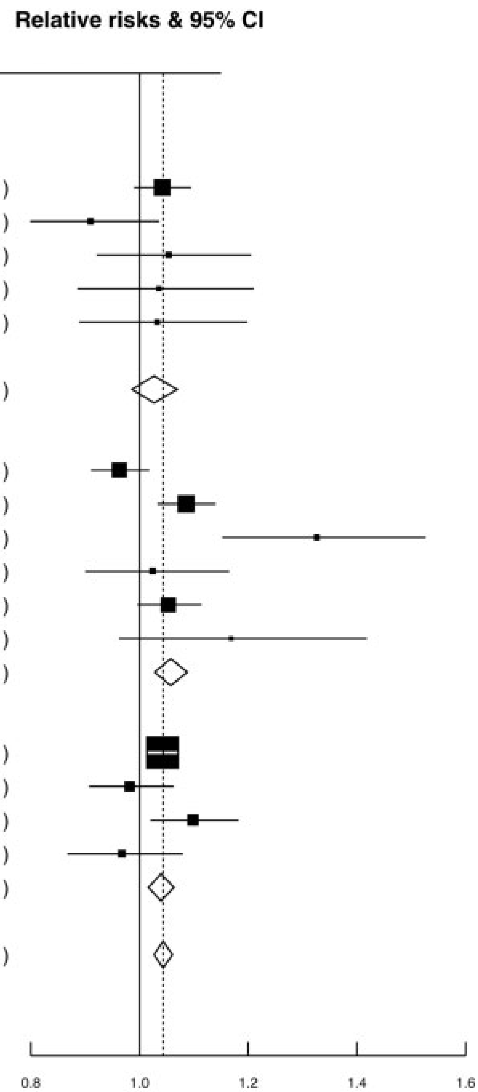
[3] *RR[2] not calculated for lack of information on sexual variables.*

Figure A6 – Relative risks (RRs) of CIN3/carcinoma *in situ* and corresponding 95% confidence intervals (CIs) by increase of 1 full-term pregnancy (FTP) and by study and study design.

Centre	Cases/ Controls	Mean age 1st FTP	RR[1]	RR[2] (95% CI)
Cohort studies				
Tromsø[3]	116/405	21.3/22.2	1.05	-
Sweden	313/306	22.9/23.6	1.04	1.04 (0.99 - 1.10)
Manchester	136/108	22.1/22.6	1.00	0.91 (0.80 - 1.04)
Portland Kaiser	39/171	22.7/23.5	1.05	1.05 (0.92 - 1.21)
Copenhagen	38/131	23.6/24.1	1.02	1.04 (0.89 - 1.21)
Guanacaste	94/446	19.0/19.9	1.05	1.03 (0.89 - 1.20)
Million Women Study[3]	456/2442	23.3/24.1	1.04	-
All cohorts	620/1162	22.5/23.3	1.04	1.03 (0.99 - 1.07)
Case-control studies - population controls				
Brinton USA	231/661	21.7/22.2	1.01	0.96 (0.91 - 1.02)
Male Factor	359/349	22.3/23.4	1.07	1.09 (1.03 - 1.14)
London CIN	109/123	21.5/26.1	1.26	1.33 (1.15 - 1.53)
Los Angeles adeno	41/280	23.2/23.5	1.02	1.02 (0.90 - 1.17)
Daling Seattle	123/1080	22.8/24.2	1.06	1.05 (1.00 - 1.11)
US Adeno	39/197	23.6/24.1	1.01	1.17 (0.96 - 1.42)
All population cc	902/2690	22.2/23.6	1.05	1.06 (1.03 - 1.09)
Case-control studies - hospital controls				
WHO studies	1396/12214	21.2/21.9	1.05	1.04 (1.02 - 1.07)
Milan in situ	222/252	24.1/24.4	1.02	0.98 (0.91 - 1.06)
IARC studies	409/464	21.2/22.7	1.08	1.10 (1.02 - 1.18)
Bangkok	69/706	21.3/23.2	1.09	0.97 (0.87 - 1.08)
All hospital cc	2096/13636	21.5/22.0	1.05	1.04 (1.02 - 1.06)
All studies	3618/17488	22.0/22.5	1.05	1.04 (1.03 - 1.06)

Heterogeneity test between studies $\chi^2_{14} = 38.72$; $p < 0.001$

Heterogeneity test between study designs $\chi^2_{2} = 1.35$; $p = 0.508$



[1] Conditioned on age at diagnosis, study or study centre.

[2] As in [1], and conditioned on age at first sexual intercourse and lifetime number of sexual partners.

[3] RR[2] not calculated for lack of information on sexual variables.

FIGURE A7 – Relative risks (RRs) of CIN3/carcinoma *in situ* and corresponding 95% confidence intervals (CIs) by 1-year decrease in age at first full-term pregnancy (FTP) and by study and study design.